

Letters to the Editor Regarding "Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study," E.T.H. Fontham, P. Correa, A. Wu-Williams, P. Reynolds, R.S. Greenberg, P.A. Buffler, V.W. Chen, P. Boyd, T. Alterman, D.F. Austin, J. Liff, and S.D. Greenberg, Cancer Epidemiology, Biomarkers & Prevention 1: 35-43, 1991.

Cancer Epidemiology, Biomarkers & Prevention published four letters concerning this article, which is a preliminary report of an ongoing U.S. case-control study that currently includes data on 420 female lung cancer cases. Fontham, et al., reported a statistically significant odds ratio for adenocarcinoma associated with spousal smoking. The series begins with a letter from Nathan Mantel, followed by a reply from the authors of the study, then continues with a letter from Peter N. Lee, also followed by a reply from the authors of the study. The letters appear in Cancer Epidemiology, Biomarkers & Prevention 1: 331-334, 1992.

Mantel stated that certain cotinine data presented in the study indicated misclassification of smoking status. Mantel also noted that possibly "extravagant" bias could be introduced in the study because next of kin provided information for 34 percent of the cases, but did so for only 10 percent of one control group. Moreover, when next of kin provided information, urinary cotinine levels could not be measured in the study participants. Finally, Mantel criticized Fontham, et al., for focusing on only adenocarcinoma, instead of treating all lung cancer cell types: "[I]f these investigators have had their choice of which type of lung cancer to emphasize, their statistical significance levels should be modified to take the multiple-testing aspect into account."

In their reply to Mantel, Fontham, et al., stated that their identification and exclusion of women with high urinary cotinine values "can only be considered a strength of the study." They also noted, with regard to the next of kin concern, that "estimates of relative risk did not differ in analyses restricted to self or proxy respondents." Finally, Fontham, et al., stated that they did not have a choice of which histological type to emphasize "because most cases turned out to be adenocarcinomas after histological review." They pointed out that the number of cases with other cell types of cancer was too small to allow reasonable statistical power in specific analyses.

Lee's letter commented that some data on cotinine and on lung cancer cell type were incomplete in this interim report. He noted that possible confounding factors (e.g., occupation, diet, medical history and other exposures) had not been taken into account. Lee said that confounding could also be due to inclusion of unmarried women in the analysis of spousal exposure, never-employed women in the analysis of occupational exposure, and to an

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unadjusted index of social exposure. According to Lee, this could lead to "an inevitable confusion of possible effects of ETS with possible effects of marital status, occupation, and sociability." Lee also stated that he calculated a relative risk for nonadenocarcinoma lung cancer which was not significantly different statistically from the relative risk for adenocarcinoma calculated by the authors. According to Lee, this failed to "justify the special attention given to the adenocarcinoma results." Finally, Lee questioned the biological plausibility of an elevated risk of adenocarcinoma associated with ETS exposure, "given that the association of active smoking with adenocarcinoma is so weak."

Fontham, et al., replied to Lee by stating that "the availability of a large data set with which to address an unresolved issue of great public health importance was compelling justification for publishing a report" that represented only three years of a five-year study. They stated that a number of potential confounders, including age, race, geographic region, respondent type, income and education had been considered, and that other potential risk factors "will be examined in further analyses." Specifically, Fontham, et al., commented on an ongoing analysis of dietary factors, and stated that β -carotene has not appeared to be related to spousal smoking habits in this study. With regard to the inclusion of unmarried women in spousal smoking calculations, Fontham, et al., calculated risk estimates with those subjects excluded that were only slightly lower than the original estimates. Exclusion of never-employed women from workplace calculations resulted in risk estimates which were elevated somewhat compared to the original calculations. Finally, Fontham, et al., defended their "special attention" to adenocarcinoma because of the large proportion of adenocarcinoma in the study. They also proposed that "exposure to sidestream smoke might result in a distribution of histological types of lung cancer different from that associated with exposure to mainstream smoke."

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